

**ARIC Manuscript Proposal #2288**

**PC Reviewed:** 1/14/14

**Status:** A

**Priority:** 2

**SC Reviewed:** \_\_\_\_\_

**Status:** \_\_\_\_\_

**Priority:** \_\_\_\_\_

**1.a. Full Title: Associations of Brain Imaging with Cognitive Change over 20 years**

**b. Abbreviated Title (Length 26 characters): Brain Imaging & Cognitive change**

**2. 2. Writing Group:** Knopman, Jack, Kantarci

Writing group members: D Knopman, C Jack, J Graff-Radford, K Kantarci, T Mosley, R Gottesman, M Griswold, AR Sharrett, G Windham, M Albert, L Coker

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. *\_DSK*

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**3. Timeline:** Complete manuscript by March 31, 2014

**4. Rationale:** There is an extensive literature on the imaging correlates of changes in cognition. For example many studies have examined associations between the vascular imaging lesions of white matter hyperintensities (WMH), infarcts (INF), microbleeds (MB) and cognitive decline. Associations with cognition are generally seen with WMH and INF but not with MBs. Investigations of whole brain volume, ventricular volume, hippocampal volume or other regions have also generally shown that brain volume is inversely related to cognitive function. Although we have examined imaging – cognition associations in ARIC using the qualitatively evaluated MR scans from 1994-6 (Mosley 2005), I do not believe we have ever examined changes in cognition versus imaging since then. There are few other longitudinal studies with cognitive testing available from middle age. With our state of the art 3T MR imaging, we are in a position of examining associations between cognition and imaging, with the unique advantage of knowledge of cognitive status from 20 years earlier.

We will conceptualize the various imaging markers to be examined into a) markers of neuronal injury (volumetric measures) and b) markers of cerebrovascular pathophysiology (WMH, INF, MB). This categorization must be used with some caution, however, because neuronal injury, and hence brain volume loss can be the result of both neurodegenerative and cerebrovascular pathophysiology. And, while INF may be a “pure” measure of cerebrovascular disease, WMH burden reflects both pathophysiology. Similarly, because MBs reflect vascular amyloid, which is moderately correlated with parenchymal amyloid, MBs abundance probably also reflects burden of Alzheimer type pathology.

The underlying conceptual model assumes that brain volume is closely related to neuronal size, neuronal numbers and synaptic density, these latter 3 being the most proximate indicators of neuronal integrity. Brain atrophy can be determined only with serial imaging; thus a single scan can measure brain volumes but can make only weak inferences about atrophy.

In this conceptualization, microinfarcts are the lesion that is the proximate arteriosclerotic cause of loss of neurons and synapses. Microinfarcts are due to lipohyalinosis and arteriolar/capillary endothelial injury and cannot be imaged by MR scanning. Only the latter is a shared pathophysiological mechanism with visible infarcts, but to the extent that both micro- and visible infarcts share common risk factors (especially hypertension and diabetes), the two types of lesions will be correlated. Visible INF are themselves moderately correlated with microinfarcts, but not strongly. The burden of neurodegenerative disease can be inferred only from the degree of brain volume loss after controlling for INF. The burden of cerebrovascular disease can be inferred from the abundance of INF and WMH. Neither measure can be considered particularly “pure” however. Note: that we will be exploring the interrelationships of the various imaging features simultaneously in a parallel investigation in ARIC ms#2266.

WMH and INF are always abnormal, but their rate of accumulation cannot be inferred from a single scan. Furthermore, WMH and INF are assumed to have a more variable relationship with both WMH and INF because both can be caused by pathologies other than small vessel endothelial injury: neurodegenerative changes and small vessel disease in the former, and small and larger vessel disease in the latter. As a consequence of their more distal relationship to neuronal injury, WMH and INF are hypothesized to have weaker relationships with cognition. Inclusion of measures of brain volumetrics in models of the relationship between WMH or INF and cognition would be expected to attenuate the associations.

The relationship is modified by subject characteristics that fall under the rubric of “cognitive reserve.” Cognitive reserve refers to an individual’s intellectual endowments, roughly proxied by education and occupation. Because ARIC collected cognitive assessments during middle age, we have a unique opportunity to employ a measure of cognitive reserve, namely ARIC visit 2 cognitive testing, alone or in combination with education and occupation.

The overall goal of these analyses is to explore the relationships between concurrent cognition and brain volumetrics, utilizing the data on initial test scores, rate of change of test scores (slope), education, occupation, and markers of cerebrovascular pathology. A secondary goal is to explore the regional specificity of the relationships depending on the cognitive test.

## **5. Main Hypothesis/Study Questions:**

A. Hypothesis: Cognitive change is associated with brain regional/global volume as measured on the ARIC-NCS MR scans, and this association is attenuated in persons with a substantial burden of concomitant cerebrovascular disease, implying that cerebrovascular disease markers are in the same causal pathway of neuronal loss. Alternative hypothesis: Cognitive change is associated with brain regional/global volume and is not attenuated by the addition of cerebrovascular imaging markers to the models.

(1) Change from visit 2 to visit 5 in scores on the delayed word recall (DWR), digit symbol substitution (DSS) and word fluency (WF) tests will be associated with global and medial temporal brain volume (for DWR) or frontal cortical thickness (for DSS and WF). Inclusion of INF but not WMH will attenuate the associations because INF is itself associated with loss of brain volume. In contrast WMH will not attenuate associations.

(2) In models of the association of change on cognitive tests to INF or WMH, burden of INF and WMH will be associated, but the inclusion of brain volume measures into the model will weaken

associations. We expect that changes in DSS and WF test scores will be more strongly associated with INF and WMH than DWR because of the known relationship between tests of psychomotor speed and cerebrovascular disease.

(3) The role of MB in associations with cognitive change is expected to be nil: the literature generally suggests there is no association between cognition and MB.

B. Models relating MRI characteristics at visit 5 to cognitive change from visit 2 to visit 5 will use models similar to those recommended in the ARIC analysis manual for exposures measured at baseline. The interpretation of findings – e.g. that WMH volume is associated with visit 2 to visit 5 decline in DSST scores – will be retrospective, with the acknowledged limitation that the temporality of the implied causal effect is not established.

We will develop separate models for associations between the 3 cognitive tests at ARIC NCS plus a global combined measure and regional and global volume measures, WMH burden, INF burden and MB burden. A first model would include age, race, sex as covariates. Model 2 will add the other imaging features.

**6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).**

a. Participants: with at least V2 and NCS cognitive data and an NCS MR scan.

b. Dependent variables: 3 ARIC cognitive tests – DWR, DSS, WF at all available time points

c. Demographic variables: age, sex, race, center, education (<high school, high school, > high school).

d. Independent variables: Using ARIC-NCS scans, brain volume (global, regional cortical thickness), WMH, infarcts, microbleeds. For these analyses, I would propose using global WMH volume, infarct counts and microbleed counts. For regional cortical thickness, I would propose 3 meta-ROI's: medial temporal lobe, AD signature regions (lateral temporal, lateral parietal, medial parietal), and a frontal one (lateral frontal, medial frontal). *(Note that for these initial analyses, there are many reasons not to attempt to use ARIC-MRI scans to calculate change: 1) the earlier scans were 1.5T and the volumetric data cannot be compared; 2) ARIC-MRI scans were done only in Jackson and Forsyth Co; hence we would lose half of cases with ARIC-NCS scans; 3) there is plenty of work to do within the current planned analyses using just the most recent 3T scans.)*

7.a. Will the data be used for non-CVD analysis in this manuscript?  Yes  No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES\_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES\_DNA = "CVD Research" would be used?  Yes  No

(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript?  Yes  No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES\_DNA = "No use/storage DNA"?  Yes  No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: <http://www.csc.unc.edu/ARIC/search.php>  Yes  No

**10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?**

ARIC ms #2266 from same author group

Mosley TH, Jr., Knopman DS, Catellier DJ *et al.* Cerebral MRI findings and cognitive functioning: the Atherosclerosis Risk in Communities study. *Neurology* 2005; 64(12): 2056-62.

Schneider AL, Sharrett AR, Patel MD *et al.* Education and Cognitive Change over 15 Years: The Atherosclerosis Risk in Communities Study. *J Am Geriatr Soc* 2012; 60(10): 1847-53.

**11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ARIC NCS:  Yes  No**

**11.b. If yes, is the proposal**

**A. primarily the result of an ancillary study (list number\* \_\_\_\_\_)**

**B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)\* 1999.01)**

\*ancillary studies are listed by number at <http://www.csc.unc.edu/aric/forms/>

**12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.**

**12b. The NIH instituted a Public Access Policy in April, 2008** which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from <http://publicaccess.nih.gov/> are posted in <http://www.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to Pubmed central.